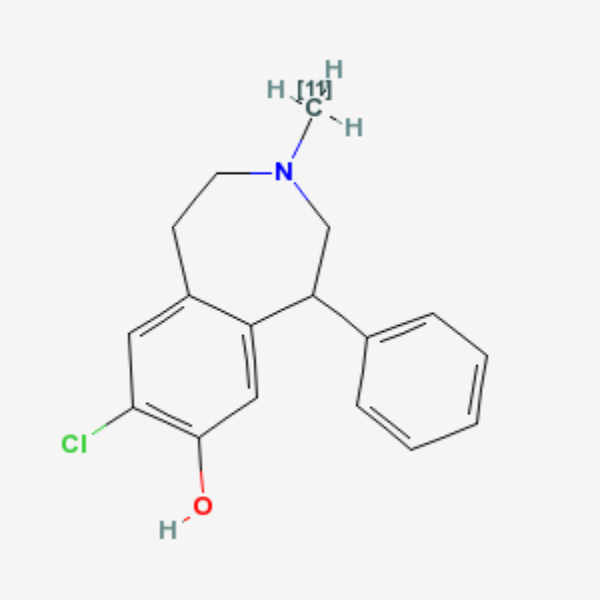
(*R*)-(+)-8-Chloro-2,3,4,5-tetrahydro-3-[^{11}C] methyl-5-phenyl-1*H*-3-benzazepin-7-ol [^{11}C]SCH 23390

Created: November 22, 2005
Updated: December 19, 2005

Chemical name: (*R*)-(+)-8-Chloro-2,3,4,5-tetrahydro-3-[^{11}C]methyl-5-phenyl-1*H*-3-benzazepin-7-ol
Abbreviated name: [^{11}C]SCH 23390, [^{11}C]SCH
Synonym:
Backbone: Compound
Target: D_1 dopamine receptors
Mechanism: Receptor binding
Method of detection: PET
Source of signal: ^{11}C
Activation: No
***In vitro* studies:** Yes
Rodent studies: Yes
Other non-primate mammal studies: No
Non-human primate studies: Yes
Human studies: Yes



Click on the above structure for additional information in PubChem [http://pubchem.ncbi.nlm.nih.gov].

Background

[PubMed]

Dopamine, a neurotransmitter, plays an important role in the mediation of movement, cognition, and emotion (1, 2). Dopamine receptors are involved in the pathophysiology of neuropsychiatric diseases such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and schizophrenia (3). Five subtypes of dopamine receptors, D_1 through D_5, have been well characterized pharmacologically and biochemically (4). These five subtypes are classified into two subfamilies: D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4) dopamine receptors. D_1-like and D_2-like receptors exert synergistic as well as opposite effects at both the biochemical and overall system level. A great majority of striatal D_1 and D_2 receptors are localized postsynaptically on caudate-putamen neurons and to a lesser extent presynaptically on nigrostiatal axons.

(*R*)-(+)-8-Chloro-2,3,4,5-tetrahydro-3-[^{11}C]methyl-5-phenyl-1*H*-3-benzazepin-7-ol ([^{11}C]SCH 23390) was found to be a selective, high-affinity antagonist of D_1 receptors, but to have only a marginal effect on D_2, α_1-adrenergic, muscarinic, and histaminergic receptors and only a slight effect on 5-HT_{2A} receptors (5). [^{11}C]SCH 23390 positron emission tomography (PET) has been used to study D_1 receptor occupancy and density in neuropsychiatric disorders and aging in humans.

Synthesis

[PubMed]

[^{11}C]SCH 23390 was synthesized by alkylation of the desmethyl compound SCH 24518 [(*R*)-(+)-8-chloro-2,3,4,5-tetrahydro-5-phenyl-1*H*-3-benzazepin-7-ol] with [^{11}C]methyl iodide (6). Reaction in acetone with subsequent normal-phase liquid chromatographic separation resulted in an 80% radiochemical yield, based on [^{11}C]methyl iodide, with a total synthesis time of 35-40 min and a radiochemical purity greater than 99%. The average specific activity was 11.1 GBq/mmol (300 Ci/mmol) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

SCH 23390 has been reported to have selective binding affinity to D_2 (striatum) and 5-HT_{2A} (frontal cortex) receptor sites in homogenates of rat brain membranes (7). The K_i values for D_1 ([^{3}H]piflutixol), D_2 ([^{3}H]spiroperidol) in the striatal membranes, and 5-HT_{2A} ([^{3}H]spiroperidol) in the cortical membranes were 1.3 nM, 880 nM, and 30 nM, respectively. SCH 23390 has a K_i value of 690 nM for the α_1-adrenergic receptor in rat forebrain membrane. The affinity for the 5-HT_{2A} receptor is about 10-fold lower than that for the D_1 receptor, suggesting that specific [^{11}C]SCH 23390 binding visualized by PET represents mainly binding to D_1 receptors. The K_d of [^{3}H]SCH 23390 was 0.53 nM for D_1(8), and the binding density (B_{max}) for D_1 was 69 pmol/g tissue.

Reported K_d values obtained with human putamen homogenates were 1.6 ± 0.22 nM for [^{3}H]SCH 23390 (1.1 ± 0.38 nM with 40 nM ketanserin, a 5-HT_{2A} antagonist) and 2.0 ± 0.2 nM for [^{3}H]raclopride, a D_2 antagonist (9). The D_1 receptor binding density (B_{max}) was 12.7 ± 3.8 and 9.9 ± 2.1 pmol/g tissue for [^{3}H]SCH 23390 without and with 40 nM ketanserin, respectively. The B_{max} of [^{3}H]raclopride for $D_{2/3}$ receptor was 13.3 ± 0.9 pmol/g tissue. In frontal cortex membranes, the B_{max} for D_1 was 6.7 ± 3.9 and 3.3 ± 0.82 pmol/g tissue without and with 40 nM ketanserin, respectively. Ketanserin had little effect on the K_d (2.1-2.4 nM). There was little specific binding of raclopride in the cortex membranes. Therefore, part of the [^{3}H]SCH 23390 binding to the putamen and frontal cortex was apparently due to 5-HT_{2A} receptor sites.

Using [^{3}H]SCH 23390 and [^{3}H]spiperone as ligands, Hyttel (10) estimated the B_{max} and K_d of dopamine D_1 and D_2 receptors in striatum in rats of different ages (from 3.5 to 25 months). The densities of the D_1 and D_2 receptors decreased with age, from 990 ± 50 and 350 ± 11 pmol/g tissue,

respectively, at 3.5 months to 690 ± 35 (30% decrease) and 240 ± 7 pmol/g tissue (31% decrease) at 25 months. However, the K_d values remained constant. The decreases in density of D_1 and D_2 receptors were parallel. Thus, the ratio between the density of D_1 and D_2 receptors remained constant throughout life.

Hess et al. (11) demonstrated that D_1 receptor density ([^{3}H]SCH 233900) was reduced by 43% in postmortem caudate brains from 8 schizophrenic patients compared with 8 normal subjects (161.4 ± 22.1 vs 281.5 ± 20.5 fmol/mg protein, respectively). In contrast, schizophrenic patients exhibited a 56% increase in D_2 receptor density, from 119.8 ± 13.7 to 186.7 ± 33.0 fmol/mg protein, as measured by [^{3}H]spiperone in the presence of 40 nM ketanserin. These resulted in a highly significant difference in the ratio of D_2/D_1 receptor density between schizophrenic patients (1.29 ± 0.29) and controls (0.42 ± 0.03).

Animal Studies

Rodents

[PubMed]

Biodistribution studies in mice showed a high accumulation of radioactivity in the intestines (1.38% injected dose (ID)/g), followed by the liver (1.06% ID/g), kidney (0.40% ID/g), lung (0.22% ID/g), and brain (0.17% ID/g) at 60 min after injection of [^{11}C]SCH 23390. There was a rapid accumulation of the tracer in the striata within the first 10 min (4.88% ID/g), followed by a slow decrease of radioactivity to 2.25% ID/g at 60 min. In contrast, radioactivity in the cerebellum decreased continuously from 1 min (3.10% ID/g) to 60 min (0.10% ID/g). The striatum/cerebellum ratios were 1.3, 3.1, 6.1, and 23.4 at 1, 10, 30, and 60 min, respectively.

Suzuki et al. (12) reported that the binding potential (B_{max}/K_d) of [^{11}C]SCH 23390 in rat striata, as measured by PET, decreased as a function of age by a maximum of 26%, whereas the binding potential of [^{11}C]raclopride decreased by 36%. These PET results confirmed that the decreases in density of D_1 and $D_{2/3}$ receptors were parallel in aging rats.

Other Non-Primate Mammals

[PubMed]

No relevant publications are currently available.

Non-Human Primates

[PubMed]

Using PET, Rosa-Neto et al. (13) directly compared the distributions of dopamine D_1 and D_2 receptors in 6 monkeys. They calculated the binding potentials of [^{11}C]SCH 23390 for dopamine D_1 receptors and [^{11}C]raclopride for dopamine D_2 receptors in monkey striatum volumes of interest, using cerebellum as a nonbinding reference region. The D_1 binding potential for [^{11}C]SCH 23390 was 1.30 ± 0.04 in monkey striata, whereas the D_2 binding potential for [^{11}C]raclopride was 1.96 ±

0.44. There were distinct gradients in the distributions of the two binding sites in monkey brain: D_1 binding predominated in the antero-ventral striatum, whereas D_2 binding was relatively greater in the dorsal-posterior striatum.

Human Studies

[PubMed]

Reported [^{11}C]SCH 23390 PET studies of D_1 receptor distribution in human brain have shown a major localization of radioactivity in the striatum. The striatum/cerebellum ratio and kinetic constants are commonly used as analytical parameters in [^{11}C]SCH 23390 PET studies, with good reproducibility (14-16). Farde et al (17). reported on [^{11}C]SCH 23390 PET studies in 2 patients with schizophrenia and in 3 normal subjects. PET brain scans of normal subjects showed a high accumulation of radioactivity in the putamen, followed by the neocortex and cerebellum, at 5-60 min after injection of 100 MBq (2.7 mCi) of [^{11}C]SCH 23390. The putamen/cerebellum ratio was 3 at 25 min. There was a marked accumulation of radioactivity in the neocortex for [^{11}C]SCH 23390 but not for [^{11}C]raclopride ($D_{2/3}$ receptors), suggesting the presence of 5-HT_{2A} binding sites. Only about 1.2% of injected [^{11}C]SCH 23390 remained in the brain at 4.5 min, and only 15% of radioactivity remained intact in blood at 42 min. PET scans of schizophrenic patients were similar to those obtained in the normal controls. [^{11}C]SCH 23390 PET was able to assess striatal dopamine receptor occupancies in patients treated with various antipsychotic drugs (18).

Suhara et al. (19) studied the effects of age on the binding of [^{11}C]SCH 23390 for D_1 receptor sites in 17 healthy male subjects 20 to 72 years of age. The binding potential of the D_1 receptors in the striatum and frontal cortex decreased with age by 35% and 39%, respectively. In another study with 8 men and 10 women (22-74 years old) (20), there were age-dependent decreases in D_1 receptor binding potential in the caudate, putamen, and occipital cortex: 6.9%, 7.4%, and 8.6% per decade, respectively. There was no difference in D_1 binding potentials between men and women.

Significant reductions in both the D_1 ([^{11}C]SCH 23390) and D_2 ([^{11}C]raclopride) binding potentials in the striatum have been observed in Huntington's disease (21-23). A great majority (90%) of patients in these studies were not on any medication affecting the dopamine and serotonin system. Medications were withdrawn for 1 to 14 days prior to PET. In patients with Parkinson's disease, there was no significant difference in D_1 receptor accumulation in the pathologic striatum compared with the contralateral striatum (24). On the other hand, there was a significant increase in D_2 binding potential in the striatum contralateral to the symptoms, compared with the opposite striatum. None of the patients was on any anti-Parkinsonism medication.

[^{11}C]SCH 23390 PET is useful for objective monitoring of D_1 receptor density and drug occupancy in patients with dopaminergic disorders. Internal dosimetry data for [^{11}C]SCH 23390 in humans are not available in the literature.

References

1. Carbon M, Ghilardi MF, Feigin A, Fukuda M, Silvestri G, Mentis MJ, Ghez C, Moeller JR, Eidelberg D. Learning networks in health and Parkinson's disease: reproducibility and treatment effects. Hum Brain Mapp 19(3):197–211; 2003. (PubMed)
2. Chesselet MF, Delfs JM. Basal ganglia and movement disorders: an update. Trends Neurosci 19(10):417–422; 1996. (PubMed)
3. Seeman P, Bzowej NH, Guan HC, Bergeron C, Reynolds GP, Bird ED, Riederer P, Jellinger K, Tourtellotte WW. Human brain D1 and D2 dopamine receptors in schizophrenia, Alzheimer's, Parkinson's, and Huntington's diseases. Neuropsychopharmacology 1(1):5–15; 1987. (PubMed)
4. Stoof JC, Kebabian JW. Two dopamine receptors: biochemistry, physiology and pharmacology. Life Sci 35 (23):2281–2296; 1984. (PubMed)
5. Hyttel J, Arnt J, van den Berghe M. Selective dopamine D1 and D2 receptor antagonists. Psychopharmacol Ser 7:109–122; 1989. (PubMed)
6. Halldin C, Stone-Elander S, Farde L, Ehrin E, Fasth KJ, Langstrom B, Sedvall G. Preparation of 11C-labelled SCH 23390 for the in vivo study of dopamine D-1 receptors using positron emission tomography. Int J Rad Appl Instrum [A] 37(10):1039–1043; 1986. (PubMed)
7. Hyttel J. SCH 23390 - the first selective dopamine D-1 antagonist. Eur J Pharmacol 91(1):153–154; 1983. (PubMed)
8. Billard W, Ruperto V, Crosby G, Iorio LC, Barnett A. Characterization of the binding of 3H-SCH 23390, a selective D-1 receptor antagonist ligand, in rat striatum. Life Sci 35(18):1885–1893; 1984. (PubMed)
9. Hall H, Farde L, Sedvall G. Human dopamine receptor subtypes--in vitro binding analysis using 3H-SCH 23390 and 3H-raclopride. J Neural Transm 73(1):7–21; 1988. (PubMed)
10. Hyttel J. Parallel decrease in the density of dopamine D1 and D2 receptors in corpus striatum of rats from 3 to 25 months of age. Pharmacol Toxicol 64(1):55–57; 1989. (PubMed)
11. Hess EJ, Bracha HS, Kleinman JE, Creese I. Dopamine receptor subtype imbalance in schizophrenia. Life Sci 40(15):1487–1497; 1987. (PubMed)
12. Suzuki M, Hatano K, Sakiyama Y, Kawasumi Y, Kato T, Ito K. Age-related changes of dopamine D1-like and D2-like receptor binding in the F344/N rat striatum revealed by positron emission tomography and in vitro receptor autoradiography. Synapse 41(4):285–293; 2001. (PubMed)
13. Rosa-Neto P, Doudet DJ, Cumming P. Gradients of dopamine D1- and D2/3-binding sites in the basal ganglia of pig and monkey measured by PET. Neuroimage 22(3):1076–1083; 2004. (PubMed)
14. Chan GL, Holden JE, Stoessl AJ, Doudet DJ, Wang Y, Dobko T, Morrison KS, Huser JM, English C, Legg B, et al. Reproducibility of the distribution of carbon-11-SCH 23390, a dopamine D1 receptor tracer, in normal subjects. J Nucl Med 39(5):792–797; 1998. (PubMed)
15. Hirvonen J, Nagren K, Kajander J, Hietala J. Measurement of cortical dopamine d1 receptor binding with 11C[SCH23390]: a test-retest analysis. J Cereb Blood Flow Metab 21(10):1146–1150; 2001. (PubMed)
16. Sossi V, Holden JE, Chan G, Krzywinski M, Stoessl AJ, Ruth TJ. Analysis of four dopaminergic tracers kinetics using two different tissue input function methods. J Cereb Blood Flow Metab 20(4):653–660; 2000. (PubMed)
17. Farde L, Halldin C, Stone-Elander S, Sedvall G. PET analysis of human dopamine receptor subtypes using 11C-SCH 23390 and 11C-raclopride. Psychopharmacology (Berl) 92(3):278–284; 1987. (PubMed)
18. Farde L, Hall H. Positron emission tomography--examination of chemical transmission in the living human brain. Development of radioligands. Arzneimittelforschung 42:260–264; 1992. (PubMed)
19. Suhara T, Fukuda H, Inoue O, Itoh T, Suzuki K, Yamasaki T, Tateno Y. Age-related changes in human D1 dopamine receptors measured by positron emission tomography. Psychopharmacology (Berl) 103(1):41–45; 1991. (PubMed)

20. Wang Y, Chan GL, Holden JE, Dobko T, Mak E, Schulzer M, Huser JM, Snow BJ, Ruth TJ, Calne DB, et al. Age-dependent decline of dopamine D1 receptors in human brain: a PET study. Synapse 30(1):56–61; 1998. (PubMed)

21. Sedvall G, Karlsson P, Lundin A, Anvret M, Suhara T, Halldin C, Farde L. Dopamine D1 receptor number--a sensitive PET marker for early brain degeneration in Huntington's disease. Eur Arch Psychiatry Clin Neurosci 243(5):249–255; 1994. (PubMed)

22. Andrews TC, Weeks RA, Turjanski N, Gunn RN, Watkins LH, Sahakian B, Hodges JR, Rosser AE, Wood NW, Brooks DJ. Huntington's disease progression. PET and clinical observations. Brain 122(Pt 12):2353–2363; 1999. (PubMed)

23. Ginovart N, Lundin A, Farde L, Halldin C, Backman L, Swahn CG, Pauli S, Sedvall G. PET study of the pre- and post-synaptic dopaminergic markers for the neurodegenerative process in Huntington's disease. Brain 120(Pt 3):503–514; 1997. (PubMed)

24. Rinne JO, Laihinen A, Nagren K, Bergman J, Solin O, Haaparanta M, Ruotsalainen U, Rinne UK. PET demonstrates different behaviour of striatal dopamine D-1 and D-2 receptors in early Parkinson's disease. J Neurosci Res 27(4):494–499; 1990. (PubMed)